Radiology

2016 New Horizons Lecture: Beyond Imaging—Radiology of Tomorrow[1]

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This article is based on the New Horizons lecture delivered at the 2016 Radiological Society of North America Annual Meeting. It addresses looming changes for radiology, many of which stem from the disruptive effects of the Fourth Industrial Revolution. This is an emerging era of unprecedented rapid innovation marked by the integration of diverse disciplines and technologies, including data science, machine learning, and artificial intelligence—technologies that narrow the gap between man and machine. Technologic advances and the convergence of life sciences, physical sciences, and bioengineering are creating extraordinary opportunities in diagnostic radiology, image-guided therapy, targeted radionuclide therapy, and radiology informatics, including radiologic image analysis. This article uses the example of oncology to make the case that, if members in the field of radiology continue to be innovative and continuously reinvent themselves, radiology can play an ever-increasing role in both precision medicine and value-driven health care.

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This article, which is based on the New Horizons lecture delivered at the 2016 Radiological Society of North America Annual Meeting, addresses looming changes for our specialty. It uses the example of oncology to make the case that, if we continue to innovate, we can play an ever-increasing role in both precision medicine and value-driven health care.

Over the past few decades, we have witnessed an accelerating convergence of life sciences, physical sciences, and computer engineering (1,2). The range of disciplines involved in health care has enlarged. Mathematicians, engineers, and data scientists are now intertwined with members of more traditional health care professions in a matrix that will only become more complex. Our role remains clear: to innovate and provide new, incremental, and evidence-based solutions to clinical problems. In performing this role, we need to be visible and active and remember that, as is often said, "If you are not at the table, you are on the menu." To maintain a place at the table, those of us in the field of biomedical imaging will need to capitalize on the unprecedented opportunities that are arising in diagnostic radiology, interventional radiology, and targeted radionuclide therapy due to advances in imaging technology, probe development, and applications of computer science, especially machine learning and artificial intelligence. In diagnostic radiology, we have been building on the foundation of anatomy and have emerged as indispensable contributors at every step of cancer care. As molecular medicine and genetics are leading innovations in cancer care, to stay current, we must now further develop molecular imaging, expanding it beyond contrast material–enhanced computed tomography (CT), magnetic resonance (MR) imaging, and fluorine 18 (^{18}F) fluorodeoxyglucose combined positron emission tomography (PET) and computed tomography (CT). It will remain essential to implement novel molecular imaging agents and determine evidence-based applications for new technologies, such as combined MR imaging and PET and hyperpolarized MR spectroscopic imaging. With the evolution of imaging technology, our reports have become more informative, but they have remained largely qualitative and descriptive. Now, we must move to structured and quantitative reporting, which are essential in the age of data science for both health care analytics and interoperability; we also need to embrace and incorporate advances from computer science, including machine learning, big data analytics, and artificial intelligence. All these elements will comprise enhanced next-generation imaging and, when paired with advances in interventional radiology and radionuclide therapy, will give our specialty an unprecedented opportunity to facilitate the practice of precision medicine.

In a visionary article published in September 2016, the president of the National Academy of Medicine, Dr Victor Dzau, and his coauthors called precision medicine "a bold concept" and "an audacious aspiration." They highlighted, however, that precision medicine remains an aspiration yet to be realized (3). The tools needed to develop precision medicine include precision diagnostics derived from molecular diagnostics, imaging analytics, big data analytics, and bioinformatics. We have the knowledge and tools to help realize the dream of precision medicine, and we need to rise to the occasion, adapt, and evolve.

Precision Oncology and Opportunities for Diagnostic Imaging

While there are many challenges to precision medicine, one of the greatest—particularly within the subfield of precision oncology—is selecting the right treatment for the right patient at the right time. As physicians, we have always strived to do this, but the tools at our disposal and our knowledge at the cellular and molecular levels in the past were comparatively limited; today, molecular-based precision medicine is within reach and has become our goal. Thus, for modern precision oncology, appropriate treatment selection requires understanding differences in the biology of different sites within and among tumors, as well as changes in tumor biology that emerge over time. Because imaging has the ability to show this spatial and temporal tumor heterogeneity, it can complement genetic and other tissue or blood-based biomarkers and serve as an in vivo companion diagnostic, playing an important role in treatment selection, treatment response assessment, and follow-up. Consider, for example, its potential to address the problem of evolutionary biology of breast cancer. It has repeatedly been shown that human epidermal growth factor receptor 2 (HER2) expression may change between the primary breast malignancy and metastases, and data suggest that up to 15% of patients with primary HER2-negative breast cancer can develop HER2-positive metastases (4). A further challenge is that not all of the metastases will necessarily be HER2 positive; thus, we need to interrogate each metastatic tumor site. Figure 1 shows a patient in whom biopsy of the primary breast cancer identified HER2-negative disease (5). As depicted, in the search for metastatic disease, CT showed an enlarged supraclavicular node, and HER2 imaging with zirconium 89 (^{89}Zr) trastuzumab PET/CT showed avid nodal uptake, indicating HER2 positivity in that node. Biopsy was performed and proved that the node was indeed HER2 positive. As a result, HER2-targeted therapy was administered, and the response was excellent (5). While the specificity of ^{89}Zr trastuzumab PET for HER2 overexpressing breast cancer and the relationship between in-vivo ^{89}Zr trastuzumab uptake and immunohistochemistry staining results (the accepted standard for treatment with HER2-targeted therapies) need to be studied further, this example shows the tremendous potential of targeted imaging to facilitate assessment of tumor heterogeneity and appropriate treatment selection (4).

To maximize our ability to distinguish between tumor types and predict tumor

https://doi.org/10.1148/radiol.2017171503

Content code: IN

Radiology 2018; 286:764–775

Abbreviation:
HER2 = human epidermal growth factor receptor 2

Conflicts of interest are listed at the end of this article.

Figure 1

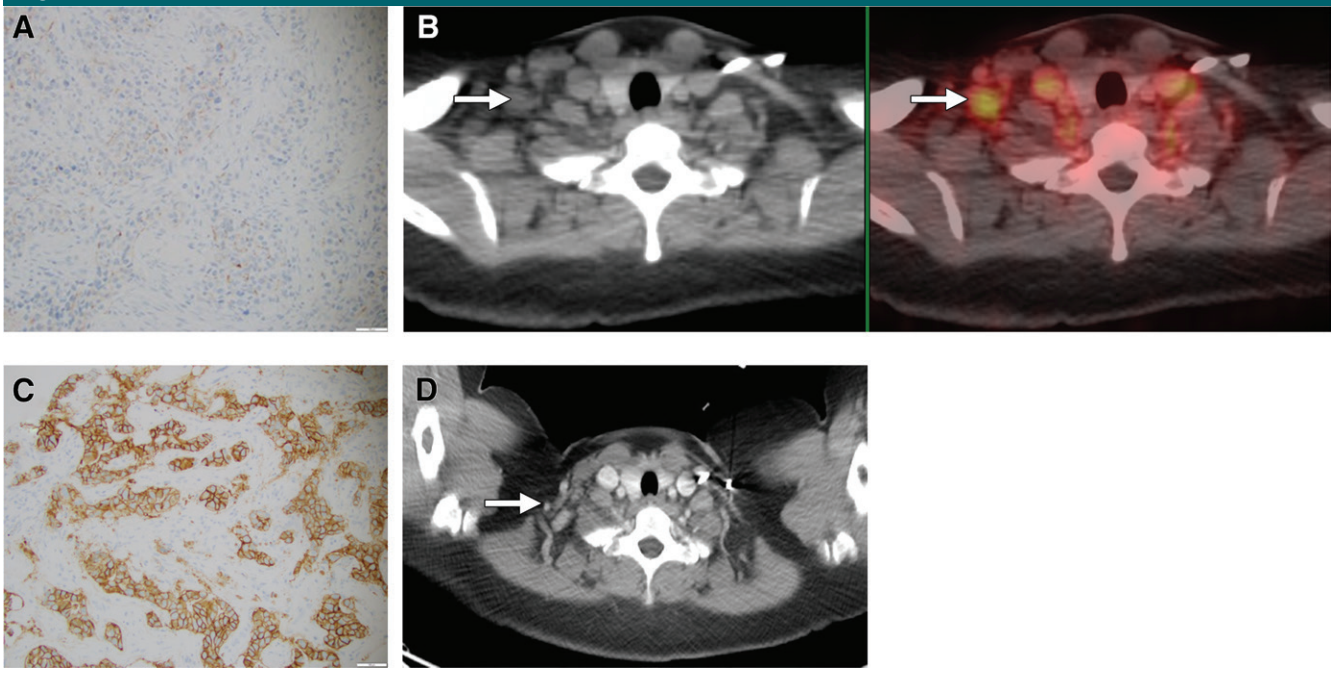


Figure 1: *A–C*, Images in a 41-year-old woman with primary estrogen receptor–positive and human epidermal growth factor receptor type 2 (HER2)-negative invasive ductal breast carcinoma and recurrence in thoracic nodes. (Reprinted, with permission, from reference 5.) *A,* Immunohistochemistry score of primary breast malignancy was 11, consistent with HER2-negative malignancy. (Original magnification, ×20.) *B,* Axial CT (left) and ^{89}Zr trastuzumab PET/CT (right) images show ^{89}Zr trastuzumab avidity in enlarged right supraclavicular nodes (arrows) (maximum standardized uptake value, 4.6) and left internal mammary nodes (not shown). *C,* Biopsy specimen of right supraclavicular node shows metastatic breast carcinoma, with an immunohistochemistry score of 31, consistent with HER2-positive disease. The patient began systemic treatment, which included administration of trastuzumab and pertuzumab. (Original magnification, ×20.) *D*, Follow-up axial CT image after 2 months of treatment shows resolution of nodes (arrow). (Image courtesy of Dr Gary Ulaner.)

behavior, we will need to understand not only tumor genotype but also its relationships to tumor phenotype, tumor metabolomics, and tumor microenvironment. We will need to move beyond genetics and develop integrated diagnostics, bringing together molecular pathology, laboratory medicine, and imaging. We must be partners in developing "next-generation diagnostics," which are diagnostics with precision measurements and quantitative expressions that, through computational analytics, will allow for development of predictive biomarkers.

An example of continuous innovations that have shed light on in vivo tumor biology with the aim of advancing clinical care is the development of a biomarker indicative of tumor metabolism: clinical carbon 13 (^{13}C) MR spectroscopic imaging using hyperpolarized [1-^{13}C] pyruvate. The first in-human study involving patients with prostate cancer showed that injection of hyperpolarized [1-^{13}C] pyruvate was safe and that imaging of hyperpolarized [1-^{13}C] pyruvate metabolism showing conversion of pyruvate to lactate was feasible (6); the study generated tremendous enthusiasm for further developing this approach to in vivo metabolic imaging among the basic science and translational imaging science communities. Multiple studies have been initiated to interrogate metabolism in a number of cancer sites, including the prostate, breast, and brain, Further research on prostate cancer expanding on the initial safety trial results is also underway. This research has shown metabolic signature repeatability and that it might be possible to grade tumor aggressiveness by using hyperpolarized imaging as a metabolic tumor biomarker (Fig 2) (7).

Advances in imaging methods are giving imaging pivotal roles at every step of cancer care, from diagnosis to treatment selection to follow-up. Figure 3 shows how information from imaging, imaging-guided biopsies (discussed in the next section), and "liquid biopsies" may be used before, during, and after treatment to enable precision oncology (8).

Advances in imaging, along with other emerging diagnostic tools of precision medicine, are already enabling notable changes in clinical trial design. Today, genetic testing is most established to select patients for molecularly targeted therapies, even though only about 10% of the patients tested are enrolled in clinical trials that target the mutation (9). The use of in vivo companion diagnostics for patient selection and assessment of pharmacokinetics is gaining acceptance. Historically, the aim of phase I clinical trials was to determine safety and tolerance and to conduct "dose finding," which is when one estimates the maximum tolerated dose that could be continued to phase II or III trials. Drug development trials are being redesigned, and there is a

Figure 2

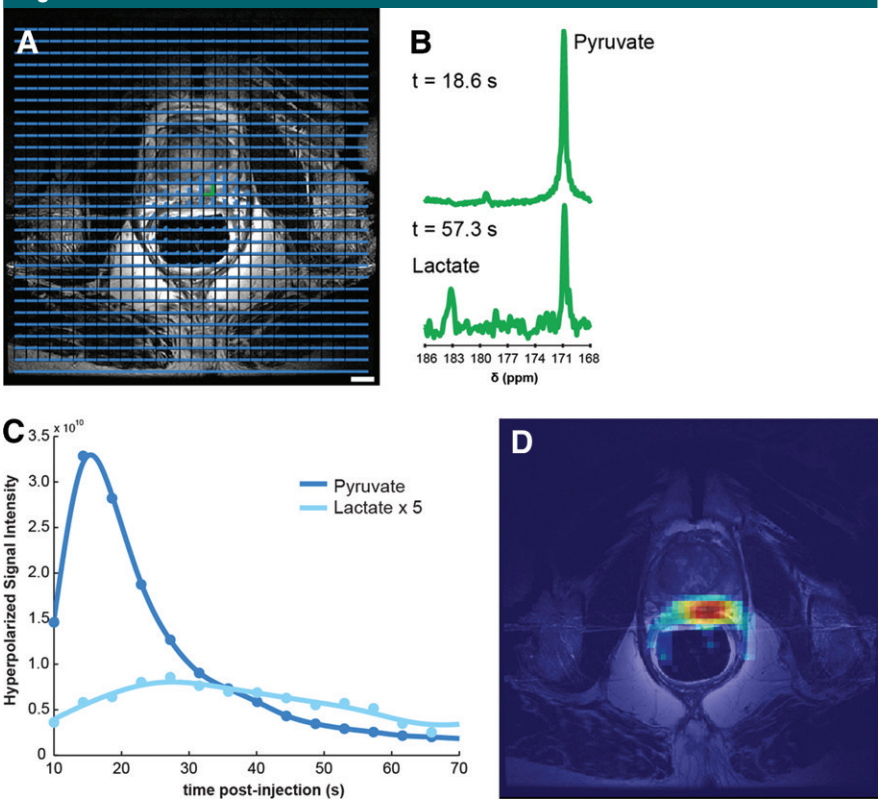


Figure 2: Images in a 71-year-old patient (prostate specific antigen level, 6.05 ng/mL). *A,* Anatomic T2-weighted MR image with an overlaid MR spectroscopic grid. White scale bar = 1 cm. *B,* Representative ^{13}C spectra at the annotated times from the voxel indicated by the green spectrum. *C,* Accompanying full dynamic curve after injection of hyperpolarized [1-^{13}C] pyruvate (244 mmol/L, 0.43 mL per kilogram of body weight). *D,* Total area under the curve of hyperpolarized lactate, the product of pyruvate metabolism, which corresponds to a region of more than 90% biopsy-proven prostate cancer (Gleason score, 3+4), and its extent. (Image courtesy of Dr Kristen Granlund.)

trend toward the merger of phase I and II trials and the identification of biomarkers that can be used to improve patient selection and dose finding. Targeted imaging shows great promise for both of these tasks. Targeted imaging has the potential to determine the biologically relevant dose, which can be used in place of the maximum tolerated dose. For example, in a phase I clinical study on the use of an androgen receptor antagonist, [(18) F]fluoro-α-dihydrotestosterone androgen receptor imaging was used in patient selection and follow-up. Dose escalation proceeded up to 480 mg, without identification of a maximum tolerated dose. However, the dose at which the treatment response reached a plateau (ie, was consistent with saturation of androgen receptor binding) proved to be just 120 mg (10). Because this was one of the first studies to use targeted molecular imaging in dose finding, the exact biologically relevant dose was not used for the phase II clinical trial. However, soon afterward, estrogen receptor imaging was used for dose finding in a phase I clinical trial of an estrogen receptor antagonist, and the targeted imaging results were used to help select the dose for phase II trials (11).

All cancer therapies–chemotherapy, targeted therapy, and immunotherapy–carry degrees of toxicity. If we can validate the use of targeted imaging to define the biologically relevant dose, we can administer smaller amounts of therapeutic agents. Furthermore, if we can select the right treatment at the outset, we can avoid unnecessary toxicity, delays in appropriate therapy, and expenses associated with ineffective treatment. Thus, through its abilities to improve treatment selection and determine biologically relevant doses, imaging can directly facilitate patient-centered value-driven precision oncology that enhances population health.

Opportunities in Interventional Radiology, Targeted Radionuclide Therapy, and Theranostics

Interventional radiology is becoming increasingly integral to patient-centered value-driven cancer care. Interventional radiology treatment approaches, such as tumor ablation and embolization, already minimize invasiveness and treatment recovery times, and with advances in imaging technology, robotics, and other areas, many interventional radiology techniques are being perfected, while new ones are being developed. Furthermore, interventional radiologists are increasingly being called on to perform "high-content" biologically targeted biopsy sampling that gathers cores of sufficient size and number for extensive molecular analyses (8).

To fully reap the benefits of modern interventional oncology, it is important to understand that we need specially trained dedicated interventional radiologists, and we need to provide them with a supportive infrastructure. It has been recognized that interventional radiologists must have clinics and admitting privileges so they can take full responsibility for the care of their patients. Furthermore, because the procedures are growing evermore complex, interventional oncology requires dedicated interventional radiology rooms with a broad array of imaging equipment. Although interventional radiology developed as a fluoroscopy-based specialty focused on angiography, more recently, cross-sectional imaging has played a larger role, and multiple imaging modalities may be needed in the same procedure. In addition, molecular imaging is already playing a critical role in determining viability after ablative procedures (12). Thus, for cutting-edge

Figure 3

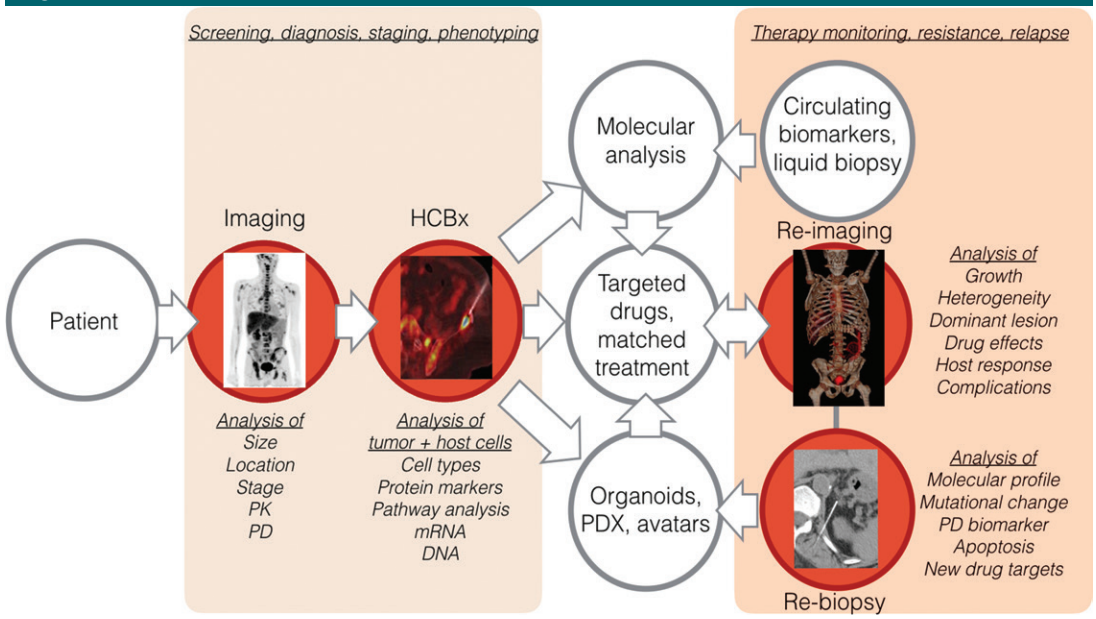


Figure 3: Advanced imaging for high-content biopsy and molecular phenotyping. In modern cancer therapy, the tumor specimen is subjected to detailed molecular analysis, including protein-, messenger RNA–, and DNA-based analyses. These molecular biomarkers are interpreted within the relevant signaling pathway to identify a potential therapeutic approach for the cancer. Selection of an appropriate therapy is dependent on detailed analysis of drug-target interactions. Drug response and development of resistance are monitored with repeat analyses. Cell lines, organoids, and patient-derived xenograft models are established at different time points to serve as avatars for drug testing, to help understand tumor biology, or both. Molecular imaging, imaging biomarkers, and image-guided biopsy (red circles) play a critical role in precision oncology. *HCBx* = high-content biopsy, *PD* = pharmacodynamics, *PK* = pharmacokinetics. (Reprinted and adapted, with permission, from reference 8.)

interventional oncology, it is increasingly important for interventional radiology rooms to include not only fluoroscopy but also cross-sectional (eg, CT, ultrasonography [US], or MR imaging) and molecular (eg, PET) imaging modalities.

Like other innovators and pioneers, interventional radiologists also need support and infrastructure for research. This research infrastructure needs to include a wet laboratory and access to small and large animals and device laboratories. When given the opportunity, interventional radiologists will continue to blaze a trail toward precision oncology.

Evidence for this assumption can be found in recent work aimed at improving precision biopsy. Collecting sufficient biopsy tissue for molecular analyses is crucial to implement appropriate targeted therapy and thus enable precision oncology. However, obtaining adequate tissue during a biopsy procedure continues to be a challenge. For example, an interim analysis of data from the National Cancer Institute Molecular Analysis for Therapy Choice (or MATCH) trial found that tumor samples in 13% of patients who underwent biopsy could not be successfully tested, a hurdle that drew attention to the issue of biopsy adequacy in the media and medical community and prompted the creation of new research funding opportunities to address it (13–15). A team effort from engineers, computer scientists, medical physicists, and interventional radiologists has made notable progress toward the development of devices for precision biopsy. One example is an in-room spectroscopic quality control tool. With this tool, every millimeter of every biopsy core undergoes spectroscopic analysis and is assessed for the presence of cancerous tissue, with the goal of ensuring sufficient tissue for genetic analysis (16). Furthermore, the spectroscopic assessments can be refined over time with machine learning (16).

Patient selection for ablative therapy is also undergoing a profound change, expanding from selection based on traditional pathology, tumor location, and tumor size to include tumor molecular properties. Patient selection for ablation is not straightforward; as with every other type of therapy, if the selection is based on only anatomic features, some patients will respond and some will not. A recent study determined that the presence of *KRAS* mutation could be used to predict local recurrence after lung cancer ablation (Fig 4) (17). As a result, in some interventional radiology practices, patients now undergo molecular testing before lung cancer ablation. If *KRAS* mutation is identified, the patient and physician make a shared decision as to whether the treatment should be changed. In a different study analyzing tumor response to radioembolization in patients with

Figure 4

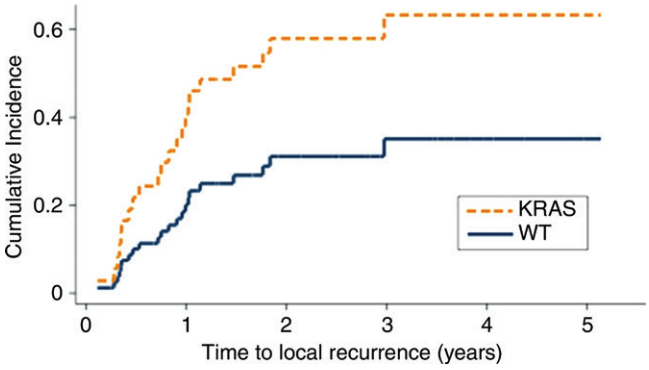


Figure 4: Graph shows cumulative incidence function of time to local recurrence, with death as a competing risk ($P = .05$) for wild-type *(WT) KRAS* versus *KRAS* mutation. (Reprinted, with permission, from reference 17.)

Figure 5

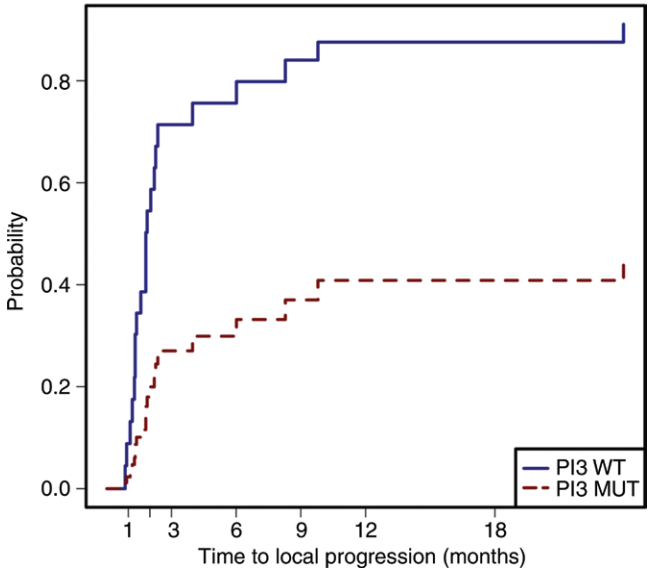


Figure 5: Graph shows time to local progression after radioembolization in patients with wild-type phosphatidylinositol 3-kinase *(PI3)* pathway and patients with mutations in the phosphatidylinositol 3-kinase pathway. *WT* = wild type. (Reprinted, under a CC BY 3.0 license, from reference 18.)

colorectal liver metastases, it was found that mutations in the phosphatidylinositol 3-kinase pathway (an intracellular signaling pathway involved in cell cycle regulation that is mutated in approximately 20% of patients with colorectal cancer) were associated with improved response to radioembolization (18) (Fig 5). In another recent study, gene expression was correlated with response to chemoembolization (19). These are the kinds of opportunities we have in interventional radiology, and when they are combined with the tools and precision of embolization and the ability to perform real-time molecular monitoring, it is obvious that interventional radiology is an important contributor to value-driven precision cancer care.

Advances in targeted radionuclide therapy and theranostics also offer those in radiology opportunities to lead. Radionuclide therapy is not new; in fact, the first article on treatment of metastatic thyroid cancer with radioactive iodine was published in 1946 (20). Today, the tools used to detect metastatic lesions, monitor treatment delivery, and provide follow-up are far more sophisticated than the ones that were available in the past. Moreover, the emerging field of theranostics, in which imaging is used to select patients for treatment, treat the disease, and monitor the response, epitomizes precision medicine. The theranostic agent that combines an imaging probe with a therapeutic entity is its own predictive biomarker. The story of revolutionary treatments of metastatic neuroendocrine cancer with dotatate is just one example of what the field promises (Fig 6) (21–23). Recently, encouraging data have been published by several groups on the treatment of castration-resistant prostate cancer with radiolabeled ligands of prostate-specific membrane antigen, which is overexpressed in patients with prostate cancer (24). While further multicenter studies are needed, reports of patients with heavily pretreated metastatic prostate cancer who have complete response at imaging and normalization of prostate-specific antigen level after treatment with radiolabeled prostate-specific membrane antigen ligands clearly suggest that theranostics may become an important treatment option in patients with prostate cancer (25,26). Continual advances in the use of nanoparticles, which offer many advantages for the design of theranostic agents, are enhancing the potential of this field (27).

If we are going to fully realize the benefits of next-generation molecular imaging and theranostics, we need to realize the importance of education and invest in the growth of a new generation of nuclear medicine physicians. Nuclear medicine physicians not only provide unique clinical services but also contribute to the advancement of the field through development of new targeted imaging probes and theranostics. Nuclear medicine physicians attend clinics and have admitting privileges; therefore, they need specialized intensive training outside the scope of diagnostic radiology. Such training will become increasingly important as the number of approved molecular imaging and theranostic agents increases and as newer imaging technologies, such as PET/MR imaging, gain greater acceptance. While there is no consensus as to whether we will ultimately have two tracks in nuclear medicine and molecular imaging—therapeutics (for nuclear physicians) and diagnostics (which could be populated by either diagnostic radiologists who complete additional training in nuclear radiology or nuclear physicians who obtain additional rigorous training in diagnostic imaging)—it is essential that we considerably expand the availability and appeal of training opportunities so we can move ahead rapidly into targeted

Figure 6

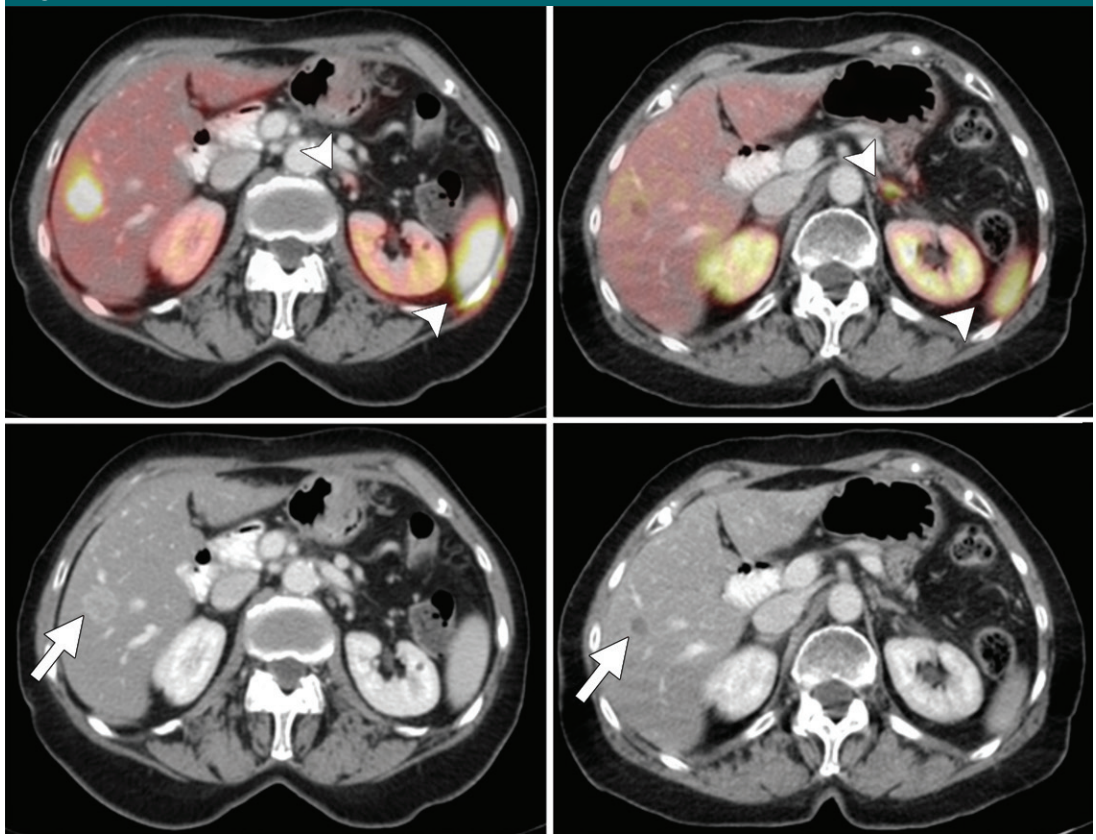


Figure 6: Gallium 68 dotatate PET/CT (top) and CT (bottom) images before (left) and 10 months after (right) the start of treatment with lutetium 177 dotatate for metastatic neuroendocrine tumor. CT images show a marked decrease in the size of the metastasis (arrows) and resolution of contrast enhancement after treatment. PET shows almost complete resolution of focal tracer uptake of the metastasis. Arrowheads indicate physiologic uptake by the spleen and left adrenal gland. (Images courtesy of Dr Wolfgang Weber.)

imaging and theranostics. One of our greatest challenges will be to attract the best and brightest physicians and offer training that is attractive to both diagnostic radiologists and, for the therapeutic track, trainees from other disciplines, such as medical oncology, pediatrics, or radiation oncology. At present, physicians who complete residency training with the current nuclear medicine curriculum have difficulty finding employment, in part because they do not have the diagnostic imaging skills to meet the expectations of many radiology practices. However, nuclear radiologists (physicians who train primarily in diagnostic imaging and perform a 1-year fellowship in nuclear radiology) are easily employed but lack the qualifications to administer parenteral therapy or conduct innovative molecular imaging research (28,29). A survey conducted for the 2011–2012 academic year in the United States found that only 144 of 201 nuclear medicine residency positions and 19 of 35 nuclear radiology fellowship positions were filled (30). We need to reinvigorate the training opportunities for nuclear medicine physicians of the future. In addition, we need to foster education and development of the radiochemists, technologists, and other personnel on whom their work depends.

Computer Science: Enhancing Precision and Efficiency to Make Radiology Stronger

There is much anxiety in the radiology community about how advances in computer science, including those in machine learning and artificial intelligence, will affect our field (31,32). However, we are not alone in this sea of rapid changes, many of which are stemming from the disruptive impact of the Fourth Industrial Revolution, an emerging era of unprecedented rapid innovations marked by the integration of diverse disciplines and technologies and a narrowing of the gap between man and machine (33). Change is imminent, and it will bring both challenges and opportunities. If we embrace computer science innovations, there are good reasons to believe that technologic advances will increase rather than reduce the importance of our profession.

Computer science tools are giving us greater efficiency, precision, and standardization, although many of them are only just starting to be explored and used. For example, informatics tools for automated tumor response assessment, which are minimizing repetitive tasks

and interreader variation, have been developed; however, for the most part, they are not yet widely distributed (34). If we consider that radiologists are often asked to obtain serial tumor response measurements for many patients in clinical trials, the benefits of this tool for productivity and efficiency are obviously tremendous. Furthermore, as the demand for volumetric measurements and total tumor burden is increasing, especially in phase I and innovative diagnostics trials (eg, analyzing relationships between liquid biopsy results and tumor morphology), the role of automated segmentation and computer-augmented measurements is increasing in importance.

Advances in computer-aided detection systems promise to dramatically increase efficiency and facilitate large-scale screening programs. The Lung Nodule Analysis 2016 (LUNA16) challenge was organized to provide an objective evaluation framework for automatic lung nodule detection algorithms by using the largest publicly available reference database of chest CT images, the Lung Image Database Consortium and Image Database Resource Initiative (or LIDC-IDRI) data set (35). An analysis of the initial results of the challenge found that some combinations of algorithms yielded sensitivity of more than 95%, with fewer than 1.0 false-positive findings per image. The best system enabled detection of nodules that were missed by expert readers who originally annotated the Lung Image Database Consortium and Image Database Resource Initiative data (35).

Another category of radiology informatics tools, those that collect data on performance metrics, can also improve efficiency by enabling continuous monitoring of and improvements in quality, safety, and patient satisfaction (36).

Big data and machine learning will also greatly enhance the informational value of existing clinical imaging techniques. For example, we are witnessing the blossoming of radiomics, a field in which digital images are converted into mineable data that can be analyzed in conjunction with other forms of data (eg, demographic, clinical, genomic, proteinomic) to identify correlations and, ultimately, discover predictive and prognostic features for improved clinical decision making (37–41). Growing numbers of publications on radiomics, as well as applications and commercially available tools for radiomics, are evidence of the emergence of this field (42–45). While we all need to be reminded that correlation does not prove causation, the potential to improve characterization, prediction, and prognostication through radiomics and other forms of big data analysis is enormous. As shown in Figure 7 for instance, analysis of radiomic features derived from MR imaging with traditional Haralick texture analysis (a method first reported in 1979 but only recently used in medical imaging) can enable better visualization of prostate cancer and its intratumoral phenotypic heterogeneity (46). Furthermore, initial data show the ability of radiomics to separate low-grade from high-grade prostate cancer (eg, Gleason score 6 lesions from Gleason score 9 lesions) at MR imaging (47), further enhancing radiologists' capacity to contribute to proper treatment selection and the implementation of precision oncology.

Another recently reported study demonstrating the potential of radiomics focused on the evaluation of mesenchymal Classification of Ovarian Cancer,

Figure 7

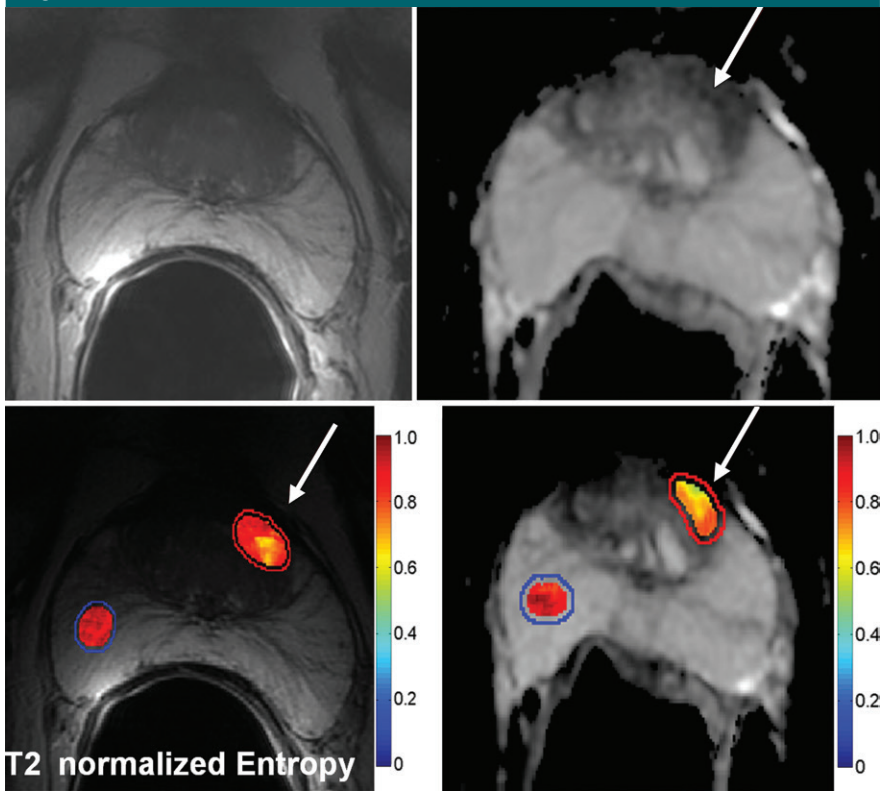
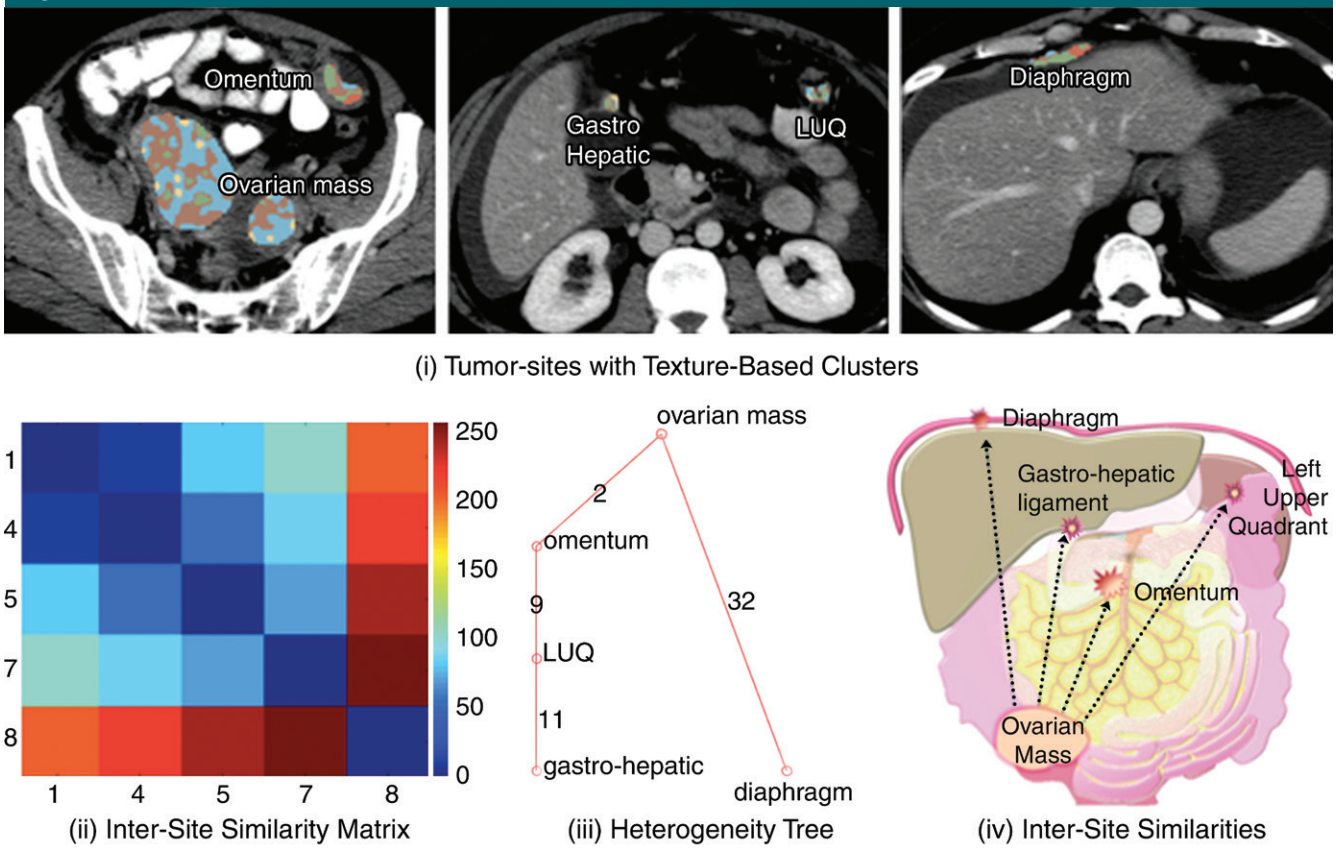


Figure 7: Application of texture analysis to T2-weighted MR images and apparent diffusion coefficient maps of prostate cancer. A lesion in the transition zone is barely discernible on the T2-weighted image (top left) and has higher conspicuity on the apparent diffusion coefficient map (top right). Texture features were computed on a per-voxel basis (using a 5×5×1 pixel window) from manually segmented regions of interest identifying the normal peripheral zone (outlined in blue) and cancer (outlined in red). From the computed texture features, a machine learning method was applied to distinguish between normal and cancerous structures and to stratify the Gleason patterns. Heat map images show clear differences between healthy tissue and cancer and depict intratumoral heterogeneity that may be useful in assessing tumor aggressiveness and informing fused MR imaging–US biopsy. (Reprinted, with permission, from reference 38.)

Figure 8



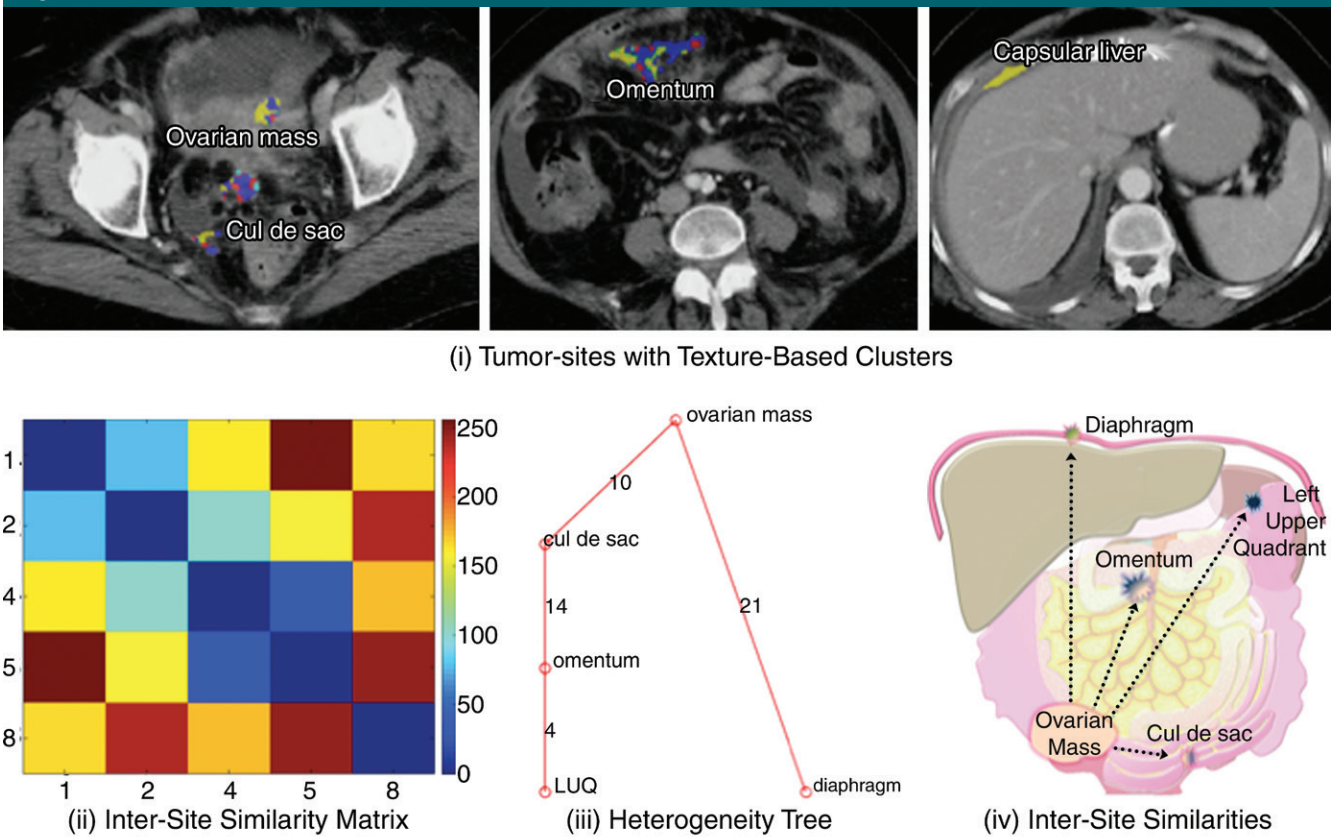
a.

Figure 8: **(a)** Patient with Classification of Ovarian Cancer mesenchymal subtype and an overall survival of 69 months. Texture-based results within each tumour site *(i)*, the intersite similarity matrix *(ISM) (ii)*, the heterogeneity tree *(iii)*, and the schematic of the dissimilarity of the various sites compared to the ovarian mass *(iv)*. For instance, the diaphragmatic tumour implant (no. 8 in *ii*) has the largest dissimilarity compared to the ovarian mass. The numbers listed in the x axis indicate the numeric codes for lesion location (*1* = primary ovarian mass, *2* = cul de sac, *4* = omentum, *5* = left upper quadrant, *7* = gastrohepatic ligament, *8* = diaphragm). (Reprinted, with permission, from reference 48.) (Fig 8 continues)

a genetic expression classification that characterizes the most lethal high-grade serous ovarian cancer (48). By applying radiomics analysis and evaluating differences in texture between primary and metastatic lesions and by using the tree-based representation of similarities, investigators found that the longer the actual physical distance was between a metastatic lesion and the primary tumor, the greater was the textural heterogeneity between the lesions (Fig 8) (48). This finding supported concepts presented in a widely quoted biology article on the trunk-branch hypothesis, which stated the complexity, dedifferentiation, and heterogeneity of metastatic lesions increased with their distance from the trunk (49). Thus, we see a continuous cycle, in which basic science and clinical research inform and validate each other. The same radiomics study also showed that intersite texture heterogeneity metrics capturing differences in texture similarities across sites were significantly associated with shorter overall survival and incomplete surgical resection (48). It is known that survival can vary for patients with the same genetic type of mesenchymal Classification of Ovarian Cancer high-grade ovarian cancer; in the study, a patient who survived only 10 months showed greater textural tumor heterogeneity than a patient who survived 69 months (Fig 8).

There is a proliferation of new methods and start-up companies addressing imaging feature extraction, machine learning, and deep learning; tools that can be used to identify clinically important features and patterns imperceptible to human cognition are emerging, and we need to embrace the new knowledge and collaborate with other disciplines to develop an array of imaging biomarkers. Those who believe machine learning will displace much of the work of radiologists and anatomic pathologists are missing something crucial: radiologists' and pathologists' primary focus is not on reading digitized images but on solving clinical problems (31). Consider the story of Iron Man: human intelligence combined with a robotic arm gave him greater precision and greater strength, and that is really

Figure 8



b.

Figure 8 *(continued)*: **(b)** Patient with Classification of Ovarian Cancer mesenchymal subtype and an overall survival of 10 months. Texture-based results within each tumour site *(i)*, the intersite similarity matrix *(ii)*, the heterogeneity tree *(iii)*, and the schematic of the dissimilarity of the various sites compared to the ovarian mass *(iv)*. For instance, the left upper quadrant *(LUQ)* (no. 5 in *b*) has the largest dissimilarity compared to the ovarian mass, followed by the diaphragmatic and the omentum tumour implants. The numbers listed in the x axis indicate the numerical codes for lesion location (*1* = primary ovarian mass, *2* = cul de sac, *4* = omentum, *5* = left upper quadrant, *7* = gastrohepatic ligament, *8* = diaphragm). (Reprinted, with permission, from reference 48.)

what machine learning and big data are to us (50). Artificial intelligence will not destroy our specialty. Rather, it will work alongside us and render our specialty more relevant than ever in delivering value-driven cancer care.

There are many predictions about the future, but there is no question that we have new knowledge and tools, that we are in the era of cognitive health, and that the partnership between humanity and technology will only become stronger. We must strive to accept the changes and evolve. New technologies should have a positive effect on our profession if we remain active and visible and, above all, remain clinicians. To borrow the words of President Roosevelt, "the only thing we have to fear is fear itself." Fear is powerful, but instead of surrendering to it, we can choose to create a future in which members of our specialty are among the leaders in precision medicine and value-driven health care.

Acknowledgments: I am grateful to Dr Andreas Hoetker, Dr Stephen B. Solomon, Dr Wolfgang Weber, and Dr Etay Ziv for their review and helpful comments. I would also like to thank Ada Muellner, MS, for her editing and Ramon E. Sosa for preparing the figures.

Disclosures of Conflicts of Interest: H.H. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: serves on the board of directors for Ion Beam Applications. Other relationships: disclosed no relevant relationships.

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